

REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claim Amendments

New claims 50-59 have been added. Support for these new claims can be found, for example, as follows:

| Claim Number | Exemplary Support |
|--------------|---|
| 50 | Original claims 17 and 2; page 50, lines 6-15 |
| 51 | Original claim 18 |
| 52-53 | Original claims 3 and 4 |
| 54-55 | Page 7. lines 1-8; page 6, lines 22-27 |
| 56-59 | Page 6, lines 17-20 |

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Rejections Under 35 U.S.C. §103

A. Gulati in view of Coffey et al. and Freshney (Paragraph 6 of the Office Action)

The rejection of claims 18, 19, 25, 27-32, 34-40, 43-46 and 49 under 35 U.S.C. §103(a) over Gulati (J. Hematotherapy 2:467-471, 1993), in view of Coffey *et al.* (Science 282:1332-1334, 1998) and Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY 1987), is respectfully traversed for the reasons set forth below.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference

teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

These criteria are not met by the present rejection. In particular, there is no suggestion or motivation to combine the references or to modify the combined reference teachings to arrive at the claimed invention, as discussed below.

The claimed invention

Claim 18 is directed to a method of preparing a cellular composition for transplantation into a recipient, comprising the steps of:

- (a) selecting a cellular composition for transplantation; and
 - (b) contacting the composition with a reovirus *ex vivo* to result in oncolysis of ras-mediated neoplastic cells;
- wherein said transplantation is autologous.

Claim 19 is also directed to a method of preparing a cellular composition for transplantation into a recipient, comprising the steps of:

- (a) selecting a cellular composition for transplantation;
- (b) contacting the composition with a reovirus *ex vivo* to result in oncolysis of ras-mediated neoplastic cells; and
- (c) administering to the transplant recipient at least one substance selected from the group consisting of anti-reovirus antibodies and immune system stimulating agents.

All other rejected claims depend ultimately from claim 18 or 19, thereby reciting all the elements of claim 18 or 19, respectively.

Teachings of the cited references

Gulati teaches that autologous stem cell transplantation has improved the long-term disease-free survival of patients with various malignancies, and purging of the stem cell graft proved to have clinical benefit. Gulati also teaches that various purging techniques are available, including positive and negative selections. Gulati, however, does not teach or suggest purging any cellular composition with reovirus.

Coffey *et al.* teach that reovirus infects cells with an activated Ras signaling pathway, and that administration of reovirus to an animal bearing a tumor with an activated Ras signaling pathway resulted in regression of the tumor. However, Coffey *et al.* do not teach or suggest treating any cellular composition with reovirus *ex vivo* for the purpose of transplanting the treated composition into an animal.

Freshney teaches a method for freezing animal cell lines by suspending the cells in culture medium containing a preservative, and freezing the resultant mixture at a low temperature. Freshney does not teach or suggest treating any cellular composition with reovirus *ex vivo* for the purpose of transplanting the treated composition into an animal.

Lack of suggestion or motivation

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references or to modify the combined reference teachings to arrive at the claimed invention. The Office Action states that it “would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a cellular composition contacted with a[sic] oncolytic reovirus for autologous transplantation because Gulati sets forth proof of clinical benefits of purging techniques” (page 4, last paragraph of the Office Action; emphasis added). Therefore, the Office Action provides a motivation to purge, rather than a motivation to combine Gulati and Coffey *et al.*

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP 2143.01. Similarly, the Federal Circuit reiterated recently that there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). Clearly, a motivation to purge, as provided here, is not a motivation to specifically combine Gulati and Coffey *et al.* to arrive at a purging technique using reovirus.

In *In re Kotzab*, the Federal Circuit found the change from the prior art to the claim invention a "technologically simple concept," but no finding "as to the specific understanding or principle within the knowledge of the skilled artisan" would have provided the motivation to modify the prior art teaching to arrive at the claimed invention. *In re Kotzab*, 55 USPQ2d at 1318. Similarly, in the present case, with the benefit of hindsight, it may seem to be a technologically simple concept to combine Gulati and Coffey *et al.* However, the use of hindsight is improper, and nothing in the references themselves or in the knowledge generally available in the art provides the required motivation or suggestion to combine Gulati and Coffey *et al.* Freshney was cited for the teaching of freezing cells in the presence of DMSO, and it does not provide any motivation or suggestion to combine Gulati and Coffey *et al.* In view of the lack of a motivation or suggestion to combine the cited references, we need not discuss the other two criteria under 35 U.S.C. §103(a).

Since the criteria under 35 U.S.C. §103(a) are not met, withdrawal of this rejection is respectfully requested.

B. Gulati in view of Coffey et al. and U.S. Patent No. 6,136,307 (Paragraph 7 of the Office Action)

The rejection of claims 18, 19, 25-29, 31-36 and 38-49 under 35 U.S.C. §103(a) over Gulati (J. Hematotherapy 2:467-471, 1993), in view of Coffey *et al.* (Science 282:1332-1334, 1998) and U.S. Patent No. 6,136,307 ("the '307 patent"), is respectfully traversed for the same reasons as set forth above.

As discussed above, there is no motivation or suggestion to combine Gulati and Coffey *et al.* The '307 patent teaches the use of reovirus to treat ras-mediated proliferative disorder, and provides no motivation or suggestion to combine Gulati and Coffey *et al.* Therefore, the present rejection does not satisfy the criteria under 35 U.S.C. §103, and its withdrawal is respectfully requested.

C. Gulati in view of Coffey et al, U.S. Patent No. 5,861,159, Freshney and U.S. Patent No. 6,136,307 (Paragraph 8 of the Office Action)

Similarly, the rejection of claims 18, 19, and 25-49 under 35 U.S.C. §103(a) over Gulati (J. Hematotherapy 2:467-471, 1993), in view of Coffey *et al.* (Science 282:1332-1334, 1998), U.S. Patent No. 5,861,159 ("the '159 patent"), Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY 1987) and U.S. Patent No. 6,136,307 ("the '307 patent"), is respectfully traversed for the lack of motivation or suggestion to combine the references.

As discussed above, there is no motivation or suggestion to combine Gulati and Coffey *et al.*, and Freshney or the '307 patent does not cure this deficiency. The '159 patent teaches methods to stimulate a systemic immune response to an antigen by administering a controlled release vehicle containing an immunopotentiating agent and the antigen. Thus, the '159 patent also provides not motivation or suggestion to combine Gulati and Coffey *et al.* Again, withdrawal of this rejection is respectfully requested since the requirement under 35 U.S.C. §103 is not satisfied.

D. Nordon et al. in view of Coffey et al. and U.S. Patent No. 6,136,307 (Paragraph 9 of the Office Action)

The rejection of claims 18, 25-29 and 38-43 under 35 U.S.C. §103(a) over Nordon *et al.* (Artificial Organs 20(5):396-402, 1996), in view of Coffey *et al.* (Science 282:1332-1334, 1998) and U.S. Patent No. 6,136,307 ("the '307 patent"), is respectfully traversed for the reasons set forth below.

The claimed invention and the requirement under 35 U.S.C. §103 have been discussed. Nordon *et al.* teach the evolving technologies required for the development of cell therapies, such as the technologies of large-scale cell separation and *ex vivo* expansion. Nordon *et al.* also teach that a cell selection step may be required to enrich a target cell population for the elimination of tumor cells, and storage of stem cells and lymphocytes for later therapy or processing is possible using cryopreservation techniques. However, Nordon *et al.* do not teach or suggest any use of reoviruses.

As previously discussed, Coffey *et al.* teach that reovirus infects cells with an activated Ras signaling pathway, and that administration of reovirus to an animal bearing a tumor with an activated Ras signaling pathway resulted in regression of the tumor. However, Coffey *et al.* do not teach or suggest treating any cellular composition with reovirus *ex vivo* for the purpose of transplanting the treated composition into an animal.

The Office Action states that it "would have been *prima facie* obvious to one of ordinary skill in the art... to prepare a cellular composition contacted with a[sic] oncolytic reovirus for autologous transplantation because Nordon provides the impetus to one of ordinary skill in the art to develop novel cell-based therapies for the treatment of malignancy and sets forth proof that *ex vivo* manipulation of cell subsets is routine in the art" (the last paragraph on page 14 of the Office Action; emphasis added). The Office Action appears to mean that Nordon *et al.* teach the benefit of cell-based therapies, and that *ex vivo* manipulation of cell subsets is within the skill in the art. Nevertheless, neither the benefit of cell-based therapies, nor whether *ex vivo* manipulation is routine, constitutes a motivation or suggestion to specifically combine Coffey *et*

al. and Nordon *et al.* It should be noted that the MPEP and case law expressly provide that the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 50 USPQ2d 1161 (Fed. Cir. 1999); MPEP 2143.01. The '307 patent has been discussed above, and it also does not provide such a motivation or suggestion. Therefore, the Office Action failed to establish a prima facie case of obviousness under 35 U.S.C. §103.

Accordingly, withdrawal of this rejection is respectfully requested.

E. Nordon et al. in view of Coffey et al., U.S. Patent No. 5,861,159 and U.S. Patent No. 6,136,307 (Paragraph 10 of the Office Action)

The rejection of claims 18, 19 and 25-49 under 35 U.S.C. §103(a) over Nordon *et al.* (Artificial Organs 20(5):396-402, 1996), in view of Coffey *et al.* (Science 282:1332-1334, 1998), U.S. Patent No. 5,861,159 ("the '159 patent") and U.S. Patent No. 6,136,307 ("the '307 patent"), is respectfully traversed for the same reasons as set forth in Section D. Specifically, there is no motivation or suggestion to combine Nordon *et al.* and Coffey *et al.*, and the '307 patent does not cure this deficiency. The '159 patent teaches methods to stimulate a systemic immune response to an antigen by administering a controlled release vehicle containing an immunopotentiating agent and the antigen. As such, the '159 patent also does not cure the deficiency of lack of motivation or suggestion to combine Nordon *et al.* and Coffey *et al.*

Accordingly, withdrawal of this rejection is respectfully requested.

Newly added claims

New claims 50-59 have been added. Claim 50 is directed to a method of preparing a cellular composition that comprises hematopoietic stem cells for transplantation into a recipient, comprising contacting the cellular composition with a reovirus *ex vivo* to result in oncolysis of ras-mediated neoplastic cells under conditions that does not alter the ability of the hematopoietic cells to differentiate into each and every hematopoietic lineage. All other new claims depend ultimately from claim 50 and hence recite all the elements of claim 50.

Applicant : Morris, *et al.*
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The new claims are not subject to any of the rejections under 35 U.S.C. §103, for the reasons articulated above. In addition, the new claims recite "under conditions that does not alter the ability of the hematopoietic cells to differentiate into each and every hematopoietic lineage", a feature not taught or suggested by any of the cited references, or any combination thereof. Therefore, the newly added claims, like the previously presented ones, are in condition for allowance.

Conclusions

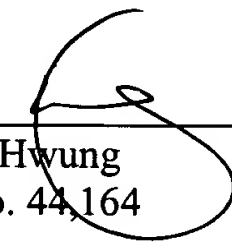
For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5044.

Enclosed is a \$90.00 check for excess claim fees. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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